

PL Subj?
Agreement

wherein the rRNA gene sequence comprises a nucleotide sequence which is at least 85% identical to SEQ ID NO: 7 or a complementary nucleotide sequence thereto.

PL 1

19. (Twice Amended) The isolated pathogenic *Leptospira* bacterium according to claim 1 having the characteristics of the microorganism deposited under AGAL Accession No. N95/69684.

PL Subj

20. (Amended) An isolated *Leptospira* bacterium consisting of *Leptospira* strain WKID (AGAL Accession No. N95/69684).

PL Subj

124. (Once amended) The isolated pathogenic *Leptospira* bacterium of claim 1, wherein said bacterium is a non-infectious or attenuated bacterium.

PL Subj

125. (Once amended) The isolated pathogenic *Leptospira* bacterium of claim 124 wherein said attenuated bacterium consists of a killed isolated bacterium.

PL Subj

126. (Once amended) The isolated pathogenic *Leptospira* bacterium of claim 124 in combination with a pharmaceutically-acceptable carrier or diluent.

REMARKS

Applicants have herein above replaced the drawings on file with new drawings pages in response to the Form PTO 948 forwarded with the Office Action mailed on March 28, 2001. Applicants respectfully submit that no new subject matter has been added to the drawings.

Claims 1-123 were pending in the instant application. In the August 24, 2000 Amendment, applicants amended claim 21 and introduced new claims 124-126 to the application. Accordingly, claims 1-126 were pending in the instant application.

Applicants have herein above canceled claims 21-74 and 76-123 without prejudice, and amended claims 1-13, 15-17, 19, 20, and 124-126. Accordingly, claims 1-20, 75, and 124-126 are now pending.

Claim 1 has been rewritten to define those *Leptospires* that serologically cross reactive to the deposited strain AGAL N95.69684. Support for new claim 1 is to be found *inter alia* in the specification at page 4, lines 1-18; and at page 5, lines 12-18.

Claim 2 has been rewritten to further define the *Leptospire* of the invention as growing in media containing 8-azaguanine and at a temperature in the range from about 13°C to about 37°C. Support for new claim 2 is to be found *inter alia* in the specification at page 6, lines 14-21.

Claims 3-13, 15-17, 19, 20, and 124-126 have been rewritten to clarify the subject matter which the applicants regard as their invention. Accordingly, support for the amendments to each of claims 3-13, 15-17, 19, 20, and 124-126 is to be found in the corresponding original claim.

A copy of the claims showing the nature and location of the amendments thereto, including [deletions] and insertions, is affixed hereto as Exhibit B and entitled "VERSION SHOWING CHANGES".

In view of the foregoing Remarks, Applicant respectfully submits that the proposed amendments to the drawings and claims introduce no new matter to the application and requests that the amendment be entered.

RESPONSE TO OFFICE ACTION MAILED ON MARCH 28, 2001

Election/Restriction

In the Office Action mailed on March 28, 2001, the Examiner acknowledged applicants' election with traverse of the Group I claims. The Examiner also deemed the restriction requirement proper and made the requirement FINAL.

Without conceding the correctness of this decision by the Examiner, Applicants have herein above canceled the non-elected claims numbered 21-74 and 76-123 from the instant application, as required.

Drawings

In the Office Action mailed on March 28, 2001, the Examiner has indicated that the drawings on file are suitable for examination purposes only. Applicants have herein above replaced the drawings at present on file with substitute drawings, affixed hereto as Exhibit A, that obviate the Draftsperson's objections to the drawings.

The Examiner is respectfully requested to acknowledge the submission of formal drawings submitted herewith.

Specification

Abstract of the disclosure

Applicants acknowledge the Examiner's comment in the March 28, 2001 Office Action that the abstract from the International application will be used in the instant application.

Title of the invention

In the Office Action mailed on March 28, 2001, the Examiner has alleged that the title of the invention is not descriptive of the invention.

In response to this objection, Applicants have herein above amended the title to read as follows:

"Leptospire pathogens having novel serology"

Applicants respectfully submit that the title as amended is descriptive of the invention as presently-claimed, by virtue of reciting the salient features of the invention, in accordance with the description at page 3, lines 9-12, of the subject specification.

The Examiner is respectfully requested to reconsider and withdraw the objection to the

title in view of this amendment.

Claim objections

In the Office Action mailed on March 28, 2001, the Examiner has objected to Claim 12 because it contains a spelling mistake.

In response to this objection, Applicants have herein above amended Claim 12 to replace "foetal" with "fetal" in Claim 12, thereby obviating this objection by the Examiner.

Claims rejections under 35 USC §112, first paragraph

In the Office Action mailed on March 28, 2001, the Examiner has rejected claims 2, 19, and 20 under 35 USC §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to those skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention.

The Examiner states that the claims are drawn on a deposit made under the provisions of the Budapest Treaty, and, as a consequence, an Affidavit or declaration by the applicants, or a statement by the attorney of record over his signature and registration number, stating that the invention will be irrevocably and without restriction released to the public upon issuance of a patent, is required to satisfy deposit requirements.

In response to this rejection by the Examiner, a statement by the attorney of record over his signature and registration number, stating that the invention will be irrevocably and without restriction released to the public upon issuance of a patent, is affixed hereto as Exhibit C.

Applicants respectfully submit that the applicants have now satisfied deposit requirements, and request the Examiner to reconsider and withdraw this rejection.

Claims rejections under 35 USC §112, second paragraph

In the Office Action mailed on March 28, 2001, the Examiner has rejected claims 1-20, 75, and 124-126 under 35 USC §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicants regard as the invention.

The Examiner states that claims 1-20, 75, and 124-126 are vague and indefinite by virtue of the recitation in Claim 1 of the term "derivative bacterium thereof". Without conceding the correctness of this rejection by the Examiner, applicants have herein above amended claim 1 to delete the phrase "or a derivative bacterium thereof" from the claim, thereby obviating this rejection. The Examiner is respectfully requested to reconsider and withdraw the rejection in light of the amendment to claim 1.

The Examiner also states that claim 2 is vague and indefinite by virtue of the

recitation of "growth characteristics" with reference to the isolated Leptospire of the invention. Without conceding the correctness of this rejection by the Examiner, applicants have herein above amended claim 2 to precisely define the growth characteristics of the subject bacterium that are intended to be encompassed by claim 2. The Examiner is respectfully requested to reconsider and withdraw the rejection in light of the amendment to claim 2.

The Examiner also states that claims 3-10 are vague and indefinite by virtue of the recitation therein of the term "capable of". Without conceding the correctness of this rejection by the Examiner, applicants have herein above amended each of the rejected claims to clearly and positively indicate the property of the isolated Leptospire of the invention that is intended to be defined by the claims. The Examiner is respectfully requested to reconsider and withdraw the rejection in light of the amendments to claims 3-10.

The Examiner also states that claim 11 is vague and indefinite by virtue of the recitation in Claim 11 of the term "reduced farrowing", because the claim fails to define the requisite level of farrowing. Without conceding the correctness of this rejection by the Examiner, applicants have herein above amended claim 11 to recite:

"The isolated pathogenic Leptospira bacterium according to claim 10, wherein the reproductive disease induced by said bacterium comprises a lower rate of farrowing in an infected animal compared to a non-infected animal."

Applicants contend that claim 11 now recites a requisite level of farrowing, by virtue of the final clause of the amended claim. The Examiner is respectfully requested to reconsider and withdraw the rejection in light of the amendment to claim 11.

The Examiner also states that claim 13 is vague and indefinite by virtue of the recitation in Claim 13 of the term "increased weaning-to-mating period", because the claim fails to define the requisite weaning-to-mating period. Without conceding the correctness of this rejection by the Examiner, applicants have herein above amended claim 13 to recite:

"The isolated pathogenic Leptospira bacterium according to claim 10, wherein the reproductive disease causes the weaning-to-mating period for the offspring of an infected animal to be longer than for the offspring of a non-infected animal."

Applicants contend that claim 13 now recites a requisite weaning-to-mating period, by virtue of the final clause of the amended claim. The Examiner is respectfully requested to reconsider and withdraw the rejection in light of the amendment to claim 13.

The Examiner also states that claim 16 is vague and indefinite by virtue of the

recitation in Claim 16 of the term "derivatives thereof". Applicants believe that this rejection is intended to be directed to Claim 17, rather than Claim 16, because there is no reference to a derivative in Claim 16. Without conceding the correctness of this rejection by the Examiner, applicants have herein above amended claim 17 to delete the phrase "or a homologue, analogue or derivative thereof" from the claim, thereby obviating this rejection. The Examiner is respectfully requested to reconsider and withdraw the rejection in light of the amendment to claim 17.

Claims rejections under 35 USC §102(a)

In the Office Action mailed on March 28, 2001, the Examiner has rejected claims 1-2 and 15-18 under 35 USC §102(a) as being anticipated by Perolat *et al* (EMBL U60594). The Examiner states that the citation teaches the entire rRNA sequence of strain Hurstbridge, described therein as a characterization and phylogenetic analysis of *Leptospira fainei* species isolated from Australian pigs.

Applicants respectfully traverse the Examiner's allegation.

Applicants submit herewith for consideration a Rule 1.132 declaration by the inventor, Roderick Chappel, affixed hereto as Exhibit C, that is considered fully responsive to this rejection by the Examiner. In particular, Dr Chappel declares that the inventor was the first to determine the 16S rRNA gene sequence disclosed by Perolat *et al*, and that the citation merely provides confirmatory sequence data. Accordingly, the date of the citation is not before the date of invention by the applicant.

Additionally, applicants direct the Examiner's attention to the fact that the isolated *Leptospire* of claim 1 as amended is a bacterium that is serologically cross-reactive to the *Leptospire* strain WKID deposited under AGAL Accession No. N95/69684. As explained in the accompanying declaration by Dr Chappel (Exhibit C), the deposited strain WKID provides a significant advantage over other strains in so far as WKID has a much lower background of autoagglutination in MAT assays than other strains, notably strain BUT6. Dr Chappel further declares that Perolat *et al* merely disclose the nucleotide sequence of 16S ribosomal RNA from *Leptospira fainei* strain BUT6, and are silent on any other strain of *L. fainei*, in particular the deposited strain WKID (AGAL N95/69684).

Furthermore, it is clear from Dr Chappel's declaration (Exhibit C) that there is a real distinction in the art between the serological grouping of bacteria and a grouping based upon nucleotide sequence identity alone. The mere disclosure of the 16S ribosomal RNA gene sequences from *L. fainei* by Perolat *et al* is therefore insufficient to enable a skilled person to isolate bacteria by their serological cross-reactivity with the deposited strain. Nor would a skilled person be even in a position to determine the serological grouping of *Leptospira* bacteria based on the mere disclosure of a single 16S ribosomal RNA gene sequence derived from a single bacterium. Accordingly, applicant respectfully submits that bacteria having serological cross-reactivity to the deposited strain constitute a novel selection invention over the Perolat disclosure. Thus, it is impossible to determine that any strain belongs to a particular serogroup or serovar without reference to the deposited strain.

For the reasons discussed in the accompanying declaration by Dr Chappel (Exhibit C), applicants respectfully submit that the pending claims are novel over Perolat's disclosure in EMBL Accession No. U60594. The Examiner is respectfully requested to reconsider and withdraw the allegation of lack of novelty over the Perolat *et al* teaching.

Claims rejections under 35 USC §102(b)

1. Hookey *et al* (EMBL Z21634)

In the Office Action mailed on March 28, 2001, the Examiner has rejected claims 1-2 and 15-18 under 35 USC §102(b) as being anticipated by Hookey *et al* (EMBL Z21634). The Examiner states that the citation teaches the entire rRNA sequence of *Leptospira inadai* strain Lyme, described therein as a phylogeny of *Leptospira* and related spirochetes.

Applicants respectfully traverse the Examiner's allegation.

Applicants submit herewith for consideration a Rule 1.132 declaration by the inventor, Roderick Chappel (Exhibit C), which is considered fully responsive to this rejection by the Examiner. In particular, Dr Chappel declares that there is no serological cross-reactivity between *L. inadai* and the strain WKID deposited under AGAL Accession No. N95/69684. Accordingly, claims 1-20, 75, and 124-126 are clearly novel over the disclosure by Hookey *et al*. The Examiner is respectfully requested to reconsider and withdraw the allegation of lack of novelty over the Hookey *et al* teaching.

2. Perolat *et al* (Abstract)

In the Office Action mailed on March 28, 2001, the Examiner has rejected claims 1-6 and 10 under 35 USC §102(b) as being anticipated by Perolat *et al* (Abstracts). The Examiner states that Perolat *et al.*, teach molecular and phenotypic characterization of Hurstbridge strains as a new genomic species of pathogenic *Leptospira*, that grows at a temperature in the range of 13° -30°C which is in between the pathogenic and saprophytic species, and on 8-azaguanine, thereby providing evidence of a serovar designated Hurstbridge. Accordingly, the Examiner considers that Perolat *et al.*, (Abstract) teaches the invention as claimed.

Applicants respectfully traverse the Examiner's allegation.

Applicants submit herewith for consideration a Rule 1.132 declaration by the inventor, Roderick Chappel (Exhibit C), which is considered fully responsive to this rejection by the Examiner. In particular, Dr Chappel declares that the abstract by Perolat *et al* (1996) does not enable the isolation and subsequent identification of the claimed genus of serologically cross-reactive Leptospires to strain WKID (N95/69684). This is because Perolat *et al* (1996) merely teach a single Leptospire isolate having the characteristics of: (i) a failure to agglutinate significantly with antisera to serovars representative of 12 recognized pathogenic serogroups; (ii) a failure of antisera raised against the isolate to agglutinate any of these 23 recognized pathogenic serovars; and a failure of the isolate to cross-agglutinate with serovars representative of recognized

saprophytic serogroups. With respect, it is apparent from Dr Chappel's declaration (Exhibit C) that any number of different Leptospires from the 25 recognized serogroups could meet the criteria of their disclosed strain, and, as a consequence, it is not possible to conclude that the isolate described by Perolat *et al* actually belongs to the serological grouping that is described and claimed in the instant application.

Moreover, it is also apparent from Dr Chappel's declaration that a serological grouping (i.e. serovar or serogroup) requires knowledge of more than a single isolate; and as a consequence, it is not possible to determine the claimed genus of bacteria that are serologically cross-reactive to the deposited strain from the general teaching provided by Perolat *et al* of a single isolate. In the present application, the serogroup that is cross-reactive to the deposited strain WKID (AGAL N95/69684) was determined based upon the provision of five isolates (see page 45 of the specification).

Moreover, it is also apparent from Dr Chappel's declaration that the teaching by Perolat *et al* of similarity between the rRNA gene sequence of strain BUT6 and the reference strains of validated genospecies (i.e. *L. interrogans*, *L. borgpetersenii*, *L. inadai*, *L. kirschneri*, *L. meyeri*, *L. noguchii*, *L. santarosai*, *L. weilii*, *L. biflexa* and *T. parva*), is insufficient to enable the isolation of a serological group of Leptospires having cross-reactivity to the deposited strain WKID (AGAL N95/69684) of the present invention, because a genetic relationship is not predicable of serological cross-reactivity. As explained by Dr Chappel, serological cross-reactivity is determined based upon criteria that are entirely distinct from rRNA gene sequence data, and cannot be determined by a non-inventive worker from a disclosure of the rRNA gene sequence.

For the foregoing reasons, and those reasons discussed in the accompanying declaration by Dr Chappel, applicants respectfully submit that the pending claims are novel over the disclosure by Perolat *et al* (Abstract). The Examiner is respectfully requested to reconsider and withdraw the allegation of lack of novelty over the Perolat *et al* (Abstract) teaching.

Claims rejections under 35 USC §103(a)

1. Perolat *et al.*, (EMBL U60594) or Hookey (EMBL Z21634) or Perolat *et al.*, (Abstracts) in view of Chappel *et al.*, (Manipulating Pig Production)

In the Office Action mailed on March 28, 2001, the Examiner has rejected claims 7 and 9 under 35 USC 103(a) as being unpatentable over Perolat *et al.*, (EMBL U60594) or Hookey (EMBL Z21634) or Perolat *et al.*, (Abstracts) in view of Chappel *et al.*, (Manipulating Pig Production). The Examiner states that it would have been obvious at the time of the invention to take the knowledge of human infection by *Leptospira* bacterium as taught by Chappel *et al.*, (Manipulating Pig Production) and apply that knowledge to the known *Leptospira* bacteria as taught by Perolat *et al.*, (EMBL U60594) or Hookey (EMBL Z21634) in view of Perolat *et al.*, (Abstracts), because Chappel *et al.*, (Manipulating Pig Production) teaches that human *Leptospira* infection is an important field of research.

Applicants respectfully traverse the Examiner's allegation.

Applicants maintain that neither Perolat *et al.*, (EMBL U60594) or Hookey (EMBL Z21634) or Perolat *et al.*, (Abstracts) teach or suggest the deposited strain WKID (AGAL N95/69684), or the serological grouping of Leptospires that are cross-reactive to the deposited strain WKID (AGAL N95/69684). Nor do these publications provide a sufficient enabling disclosure for a skilled non-inventive worker to determine such a serological grouping. Nor does the disclosure by Chappel *et al.*, (Manipulating Pig Production) mention or suggest the serological grouping of the invention.

With respect, all that Perolat *et al.*, (EMBL U60594) or Perolat *et al.*, (Abstracts) in view of Chappel *et al.*, (Manipulating Pig Production) would possibly render obvious is the ability of a single isolated "BUT6" strain to cause leptospirosis in humans. Similarly, all that Hookey (EMBL Z21634) in view of Chappel *et al.*, (Manipulating Pig Production) possibly teaches is the ability of *L. inadai* serovar Lyme, which is *not* serologically cross-reactive with the claimed serogroup of Leptospires that are cross-reactive with *L. fainei* strain WKID (AGAL N95/69684), to cause leptospirosis in humans. Accordingly, in contrast to the Examiner's assertion, the claimed serological grouping is not evident to the non-inventive skilled person, based upon these combined disclosures.

Thus, applicants maintain that the invention as claimed is clearly inventive over Perolat *et al.*, (EMBL U60594) or Hookey (EMBL Z21634) or Perolat *et al.*, (Abstracts) in view of Chappel *et al.*, (Manipulating Pig Production).

Applicants respectfully request the Examiner to reconsider and withdraw the allegation that the invention is obvious in light of the foregoing argument, and the accompanying Chappel Declaration, and the instant amendment to the claims.

2. Perolat *et al.*, (EMBL U60594) or Hookey (EMBL Z21634) or Perolat *et al.*, (Abstracts) in view of Chappel *et al.*, (Pig Research Report)

In the Office Action mailed on March 28, 2001, the Examiner has rejected Claims 8, 11-14 under USC 103(a) as being unpatentable over Perolat *et al.*, (EMBL U60594) or Hookey (EMBL Z21634) or Perolat *et al.*, (Abstract) in view of Chappel *et al.*, (Pig Research Report). The Examiner states that Chappel *et al.*, (Pig Research Report) teach that infection of *Leptospira* can cause infertility, abortions, still births and is associated with seasonal infertility (page 3); that serovars can also cause early embryonic loss, however vaccination against the *bratislava* serovar can improve the farrowing rate in herds (page 6); that isolates used in the study were grown at 13°C in the present of 8-azaguanine (page 4), and that a partial sequence of the 16S ribosomal RNA gene was obtained and sequence homology was compared (page 4); that other research methods detect *Leptospira* from bovine urine (page 5); that a previously undiscovered *Leptospire* serovar which is a member of the pathogenic species *Leptospira inadai* and a serovar within the *L. inadai* (page 5); and that several pigs had the Hurstbridge serovar (page 13). The Examiner concludes that no more than routine skill would have been required to use known infection capabilities of *Leptospira* as taught by Chappel *et al.*, (Pig Research Report) with the isolated *Leptospira* bacterium of Perolat *et al.*, (EMBL U60594) or Hookey (EMBL Z21634) or Perolat *et al.*, (Abstracts) because Chappel *et al.*, (Pig Research Report) teaches that reproductive problems are well known to be associated with *Leptospira* infections in

pigs and bovines.

Applicants respectfully traverse the Examiner's allegation.

Applicants maintain that neither Perolat *et al.*, (EMBL U60594) or Hookey (EMBL Z21634) or Perolat *et al.*, (Abstracts) teach or suggest the deposited strain WKID (AGAL N95/69684), or the serological grouping of Leptospires that are cross-reactive to the deposited strain WKID (AGAL N95/69684). Nor do these publications provide a sufficient enabling disclosure for a skilled non-inventive worker to determine such a serological grouping. Nor does the disclosure by Chappel *et al.*(Pig Research Report) mention or suggest the serological grouping of the invention.

With respect, all that Perolat *et al.*, (EMBL U60594) or Perolat *et al.*, (Abstracts) in view of Chappel *et al.*(Pig Research Report) would possibly render obvious is the ability of a single isolated "BUT6" strain to cause reproductive disease in pigs and bovines. Similarly, all that Hookey (EMBL Z21634) in view of Chappel *et al.*(Pig Research Report) possibly teaches is the ability of *L. inadai* serovar Lyme, which is serologically non-reactive with the claimed serogroup of Leptospires that are cross-reactive with *L. fainei* strain WKID (AGAL N95/69684), to cause reproductive disease in pigs and bovines. Accordingly, in contrast to the Examiner's assertion, the claimed serological grouping is not evident to the non-inventive skilled person, based upon these combined disclosures.

Thus, applicants maintain that the invention as claimed is clearly inventive over Perolat *et al.*, (EMBL U60594) or Hookey (EMBL Z21634) or Perolat *et al.*, (Abstracts) in view of Chappel *et al.*(Pig Research Report).

Applicants respectfully request the Examiner to reconsider and withdraw the allegation that the invention is obvious in light of the foregoing argument, and the accompanying Chappel Declaration, and the instant amendment to the claims.

3. Perolat *et al.*, (EMBL U60594) or Hookey (EMBL Z21634) or Perolat *et al.*, (Abstracts) in view of Haake *et al.*(USSN 5,643,754)

In the Office Action mailed on March 28, 2001, the Examiner rejects Claims 5-8, 10, 12, and 124-126 under 35 USC 103(a) as being unpatentable over Perolat *et al.*, (EMBL U60594) or Hookey (EMBL Z21634) or Perolat *et al.*, (Abstracts) in view of Haake *et al.* The Examiner states that Haake *et al.* teach that leptospirosis is a widespread zoonotic disease caused by pathogenic strains of Leptospira that are capable of infecting most mammalian species (col. 1 lines 20-25); that infection in livestock causes loss due to abortion, stillbirth, infertility, decreased milk production and death (col. 1 lines 27-30); that Leptospira proteins may be comprised in pharmaceutical compositions useful for inducing immune responses in animals (col. 7 lines 30-34); and that preparations include sterile or aqueous or non-aqueous solutions, suspension, emulsions and other like examples (col. 7 lines 45-50). The Examiner considers that it would have been obvious at the time of applicants invention to combine Leptospira with a pharmaceutically acceptable diluent as taught by Haake *et al.*, with the bacterium of Perolat *et al.*, (EMBL U60594) or Hookey (EMBL Z21634)

or Perolat *et al.*, (Abstracts) because Haake *et al.* states that such compositions may induce an immune response in animals.

Applicants respectfully traverse the Examiner's allegation.

Applicants maintain that neither Perolat *et al.*, (EMBL U60594) or Hookey (EMBL Z21634) or Perolat *et al.*, (Abstracts) teach or suggest the deposited strain WKID (AGAL N95/69684), or the serological grouping of Leptospires that are cross-reactive to the deposited strain WKID (AGAL N95/69684). Nor do these publications provide a sufficient enabling disclosure for a skilled non-inventive worker to determine such a serological grouping. Nor does the disclosure by Haake *et al.* mention or suggest the serological grouping of the invention.

With respect, all that Perolat *et al.*, (EMBL U60594) or Perolat *et al.*, (Abstracts) in view of Haake *et al.* would possibly render obvious is a composition comprising a single isolated "BUT6" strain for use in the treatment of leptospirosis. Similarly, all that Hookey (EMBL Z21634) in view of Haake *et al.* possibly teaches is a composition comprising *L. inadai* serovar Lyme, which is serologically non-reactive with the claimed serogroup of Leptospires that are cross-reactive with *L. fainei* strain WKID (AGAL N95/69684), to cause reproductive disease in pigs and bovines. Accordingly, in contrast to the Examiner's assertion, the claimed serological grouping is not evident to the non-inventive skilled person, based upon these combined disclosures.

Thus, applicants maintain that the invention as claimed is clearly inventive over Perolat *et al.*, (EMBL U60594) or Hookey (EMBL Z21634) or Perolat *et al.*, (Abstracts) in view of Haake *et al.*.

Applicants respectfully request the Examiner to reconsider and withdraw the allegation that the invention is obvious in light of the foregoing argument, and the accompanying Chappel Declaration (Exhibit C), and the instant amendment to the claims.

Conclusion

In view of the foregoing Amendments and Remarks, Applicants respectfully submit that the instant application is now in condition for allowance, which action is earnestly solicited by the Applicants.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: 9/27/01

By: Mark R. Benedict
Mark R. Benedict
Registration No. 44,531
Attorney of Record
620 Newport Center Drive
Sixteenth Floor
Newport Beach, CA 92660